

### **REMARKS**

Applicants respectfully request the Examiner to reconsider the present application in view of the following remarks.

#### ***Status of the Claims***

Claims 1-6 are currently pending in the present application. The Office Action is Final. No new amendments to the claims are proposed, thus no new matter has been added.

Based upon the above considerations, entry of the present Response is respectfully requested.

#### ***Rejection Under 35 U.S.C. § 103(a)***

Claims 1-6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown *et al.* (U.S. Patent Application Publication No. 2003/0166282, hereinafter "Brown *et al.*") further in view of Burgess *et al.*, "Syntheses of Nucleoside Triphosphates," Chemical Reviews, 100:2047-2059 (2000) (hereinafter "Burgess *et al.*").

The Examiner suggests that Brown *et al.* teaches the feasibility and availability of making and synthesizing RNA containing 4'-thioribonucleoside triphosphate. Further, the Examiner asserts that Brown *et al.* teaches the advantage and benefit of 4'-thioribonucleoside triphosphates such that they increase inhibitory activity of siRNA molecules.

The Examiner also suggests that contrary to Applicants' assertions, one of ordinary skill in the art would have been sufficiently motivated to try different synthesis methods of Burgess *et al.* and ultimately arrive at the claimed invention without undue experimentation, because

Burgess *et al.* expressly taught, “Chemists wishing to prepare nucleoside triphosphates with a minimum amount of effort should refer to the procedures listed above...Improved solid-phase syntheses amenable to automation or genuinely combinatorial approaches would be particularly timely.” See page 2058. (emphasis added)

Additionally, the Examiner suggests that since the methods of synthesizing and incorporating 4'-thioribonucleoside-triphosphates as well as the benefits conferred by the 4'-thioribonucleoside-triphosphates were known in the art at the time of the invention as taught by Brown *et al.*, and since a finite number of available methods of synthesizing nucleoside triphosphates for different nucleobase derivatives were known in the art at the time of the invention as taught by Burgess *et al.*, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success. Further, the Examiner asserts that since Burgess *et al.* taught that any chemist could amend or combine the different approaches of preparing nucleoside triphosphates with a minimum amount of effort, a person of ordinary skill in the art would have had a reasonable expectation of success in making the claimed invention at the time the invention was made. Applicants respectfully traverse.

Reconsideration and withdrawal of this rejection is respectfully requested based on the following considerations.

The Examiner admits that Applicants are correct that Brown *et al.* does not teach 4'-thioribonucleoside or 4'-thio-2'-deoxyribonucleoside, wherein the ribonucleoside is adenine, guanine, cytosine, or hypoxanthine as in the instant case.

The modified nucleotide disclosed in Brown *et al.* at [0050] is 4-thio-UTP. According to the generally accepted chemical nomenclature, this abbreviation means that the sulfur atom is

present on the 4-position on the base, instead of the sugar. It is clearly not a typographic error for "4'-thio", because 2-thio-CTP, 2'NH<sub>2</sub>-UTP, 2'NH<sub>2</sub>-CTP and 2'F-UTP are also disclosed in the same paragraph. Thus, Brown *et al.* does not disclose a 4'-thionucleoside. In addition, Brown *et al.* discusses only phosphodiester and base modifications, but does not mention or suggest modifications on the sugar.

With regard to the Examiner's comments regarding Burgess *et al.*:

"Chemists wishing to prepare nucleoside triphosphates with a minimum amount of effort should refer to the procedures listed above...Improved solid-phase syntheses amenable to automation or genuinely combinatorial approaches would be particularly timely."

Applicants respectfully believe that the Examiner takes the comments out of context.

The paragraphs actually read:

No method for preparing nucleoside triphosphates is suitable for all nucleobase derivatives. This is unfortunate because in this evolving age of genomic drug discovery, the need for nucleoside triphosphates will increase. Current applications for these materials include DNA sequencing, therapeutic nucleoside inhibitors of polymerases, and in vitro transcription procedures to prepare aptamers; this list is likely to expand.

Landmarks in the development of contemporary syntheses of nucleoside triphosphates include: Yoshikawa's POCl<sub>3</sub> phosphorylation procedure to give nucleoside monophosphates (section 3.1); Ludwig's "one-pot, three-step" triphosphorylation procedure (Scheme 2); various protocols for activating monophosphates then reacting them with pyrophosphate, e.g., Bogachev's procedure (Scheme 15); and the Ludwig-Eckstein procedure involving an activated phosphite (section 6, Scheme 18).

Chemists wishing to prepare nucleoside triphosphates with a minimum amount of effort should refer to the procedures listed above.

Some research innovations could greatly facilitate syntheses of nucleoside triphosphates. Improved solid-phase syntheses amenable to

automation or genuinely combinatorial approaches would be particularly timely. Direct, one-step triphosphorylation procedures, for instance, wherein a triphosphate entity is added as a nucleophile, would also be valuable. Perhaps a rate-limiting feature of development of new methods is availability of protected and/ or stabilized triphosphate and diphosphate building blocks. We feel that Todd's early work along these lines has not been paid sufficient attention. Finally, enzymatic procedures have proved to be excellent for biochemical purposes and for some syntheses of purified nucleoside triphosphates. This is another area of potential development.

In summary, methods for syntheses of nucleoside triphosphates evolved rapidly in the 1950s, but efforts in this area have tapered off, and for the past decade they have languished. A revival of interest in preparations of these important molecules would be appropriate.

This commentary does not describe any particular synthesis improvement or innovation, but is merely a wish list of future enhancements to the technology that the authors would like to see since current methodologies are limited in practical application.

As discussed in the October 9, 2007 response, Burgess *et al.* describes that nucleoside triphosphates are difficult to make, isolate characterize and store (*See Burgess et al.*, page 2048, section 2 - General Practical Considerations). Also, Burgess *et al.* indicates that despite the popularity of nucleoside triphosphate syntheses that involve reaction with  $\text{POCl}_3$ , then with pyrophosphate, the method is not perfect and is not successful for all nucleoside derivatives (*Id.* at pg. 2050, column 2, fourth paragraph). Analysis of the reactions also indicates that reaction times are variable and at certain steps the reactions are not perfectly selective to particular intermediates (*Id.*). Additionally, the reactions indicated within Burgess *et al.*, do not involve thio-nucleosides which further complicates whether the reactions are applicable to thio-nucleosides.

Combined with the full commentary described above in context, one skilled in the art would not be motivated by the combination of Brown *et al.* and Burgess *et al.* to make the 4'-thionucleoside of the present invention.

Any cited reference used for a rejection under 35 U.S.C. § 103(a) must be considered in its entirety, *i.e.*, as a whole, including those portions that would lead away from a claimed invention. See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). In other words, the Burgess *et al.* reference must be read in its entirety, including the teaching away that “no method for preparing nucleoside triphosphates is suitable for all nucleobase derivatives,” the complexities described in the synthesis reactions, and no showing of a thio base nucleoside reaction within Burgess *et al.*

As such, there would be no reasonable expectation for success to do that which Applicants have done based on the cited references.

Accordingly, with regard to the 4'-thio nucleoside of the present invention, one skilled in the art would not have arrived to the present invention with the combination of Brown *et al.* and Burgess *et al.*

Even if one was motivated to modify the prior art (a point not conceded), the evidence discussed above clearly establishes that there are not a “limited number of predictable solutions” as required by *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (U.S. 2007).

**CONCLUSION**

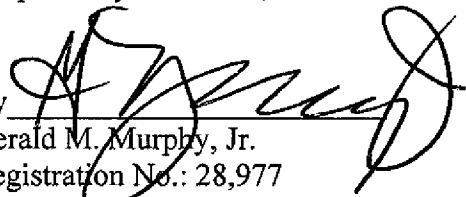
In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59, 228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§ 1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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